Developmental heterogeneity of cardiac fibroblasts does not predict pathological proliferation and activation.

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Public Summary:
• Cardiac fibroblasts are a developmentally heterogeneous population, reported to have embryonic origins from the hematopoietic system, endothelium, epicardium, and neural crest. • Cardiac fibroblasts play a key role in regulating normal myocardial integrity, as well as reverse remodeling that occurs after injury. • Reactivation of certain developmental gene programs might prime a subset of fibroblast to be preferentially activated after myocardial injury. • We characterize a combination of surface markers that can be used to prospectively identify and isolate the majority of cardiac fibroblasts using FACS (fluorescence-activated cell sorting). • The cardiac fibroblast pool is primarily derived from the epicardial and endothelial lineages, with no ostensible contribution from hematopoietic or circulating cells. • On injury, cardiac fibroblasts from different lineages exhibit similar proliferation rates and gene expression patterns, suggesting that cardiac fibroblasts are

Scientific Abstract:
RATIONALE: Fibrosis is mediated partly by extracellular matrix-depositing fibroblasts in the heart. Although these mesenchymal cells are reported to have multiple embryonic origins, the functional consequence of this heterogeneity is unknown. OBJECTIVE: We sought to validate a panel of surface markers to prospectively identify cardiac fibroblasts. We elucidated the developmental origins of cardiac fibroblasts and characterized their corresponding phenotypes. We also determined proliferation rates of each developmental subset of fibroblasts after pressure overload injury. METHODS AND RESULTS: We showed that Thy1(+)CD45(-)CD31(-)CD11b(-)Ter119(-) cells constitute the majority of cardiac fibroblasts. We characterized these cells using flow cytometry, epifluorescence and confocal microscopy, and transcriptional profiling (using reverse transcription polymerase chain reaction and RNA-seq). We used lineage tracing, transplantation studies, and parabiosis to show that most adult cardiac fibroblasts derive from the epicardium, a minority arises from endothelial cells, and a small fraction from Pax3-expressing cells. We did not detect generation of cardiac fibroblasts by bone marrow or circulating cells. Interestingly, proliferation rates of fibroblast subsets on injury were identical, and the relative abundance of each lineage remained the same after injury. The anatomic distribution of fibroblast lineages also remained unchanged after pressure overload. Furthermore, RNA-seq analysis demonstrated that Tie2-derived and Tbx18-derived fibroblasts within each operation group exhibit similar gene expression profiles. CONCLUSIONS: The cellular expansion of cardiac fibroblasts after transaortic constriction surgery was not restricted to any single developmental subset. The parallel proliferation and activation of a heterogeneous population of fibroblasts on pressure overload could suggest that common signaling mechanisms stimulate their pathological response.